REMARKS

Claims 1-25, 52-58, and 62-86 are pending. Claim 1 is amended with this reply. Claims 1 and 62 are independent. Support for the amendments can be found throughout the specification. No new matter has been added. Applicants thank the Examiner for withdrawing prior rejections of the claims.

Rejections under 35 U.S.C. § 103(a)

Monforte in view of Koster

Claims 1-13, 15, 52-58, 62-74, and 76 have been rejected as being obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,830,655 to Monforte et al. ("Monforte '655") in view of U.S. Patent No. 6,043,031 to Koster et al ("Koster"). See the Office Action at 3-10. Claims 2-13 depend from claim 1; claims 63-74 and 76 depend from claim 62.

Claim 1 relates to a probe array including an array surface, a first cleavage product of a first probe molecule which includes a label, and a second cleavage product of the first probe molecule which is immobilized on the array surface. The first cleavage product is bound to a first region of a target molecule, and the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. The second cleavage product is bound to a second region of the target molecule. The array also includes a cleavage product of a second probe molecule immobilized on the array surface at a second defined site, wherein the cleavage product of the second probe molecule is not bound to a target molecule. The cleavage products of the first and second probe molecules are in contact with a cleaving solution. See independent claim 1.

Claim 62 relates to a probe array including an array surface, a first probe molecule immobilized on the array surface having a label and a selectively cleavable bond between the site of immobilization on the array surface and the label, where the first probe molecule is bound to a corresponding target molecule. A second probe molecule is also immobilized on the array surface, and has a label and a selectively cleavable bond between the site of immobilization on

the array surface and the label. The second probe molecule is not bound to a corresponding target molecule. The first and second probe molecules are in contact with a cleaving solution. See independent claim 62.

The probe arrays of claim 1 and claim 62 each include probe molecules (or cleavage products of probe molecules) **bound to** target molecules and in contact with a cleaving solution.

Monforte '655 describes modified oligonucleotide primers. The primers can be immobilized. The primers can be extended from their 3' ends and subsequently cleaved from an immobilized 5' end. See Abstract. The Examiner argues that Monforte '655, at FIG. 16 (reproduced below for reference), teaches "target molecule 133 hybridized to immobilized first probe molecule bearing cleavage site 127 bound to a target (column 18, lines 25-67)."

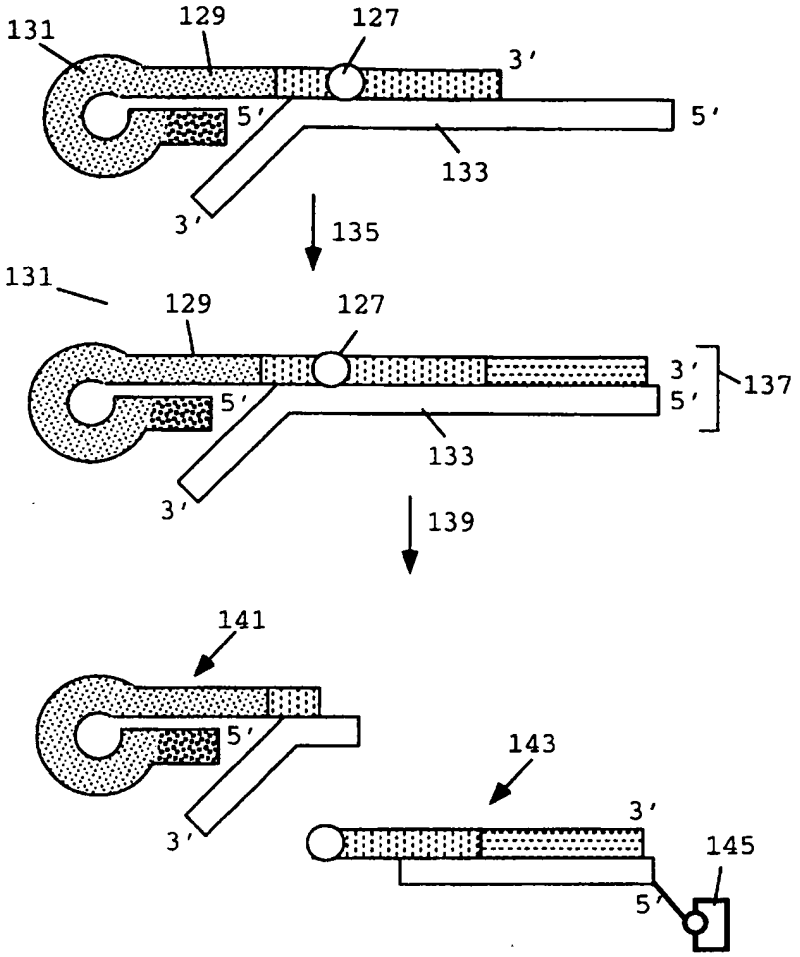
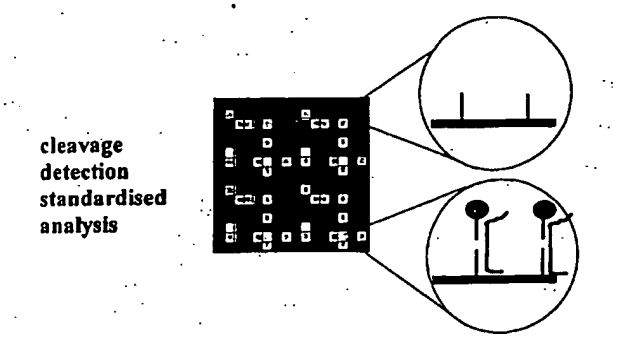


Fig. 16

Furthermore, "the two separate fragments at the bottom of Figure 16 are cleaved but still annealed to one another, and comprising the first target region bound to first cleavage product and comprising the label, and the second target region which is bound to the second region of the probe which is still immobilized to array surface 145." The Examiner further notes that "the claim does not require the target to be uncleaved." Office Action at paragraph 10.

Finally, Monforte '655 does "not explicitly teach two different probes on the array surface." Koster "teach[es] the known technique of having multiple different sequences in an array." *Id.*

Applicants note an important structural distinction between the oligonucleotides depicted in Applicants' FIG. 7 and those in FIG. 16 of Monforte '655. A detail of Applicants' FIG. 7 is provided below for reference.



Applicants' oligonucleotides, as illustrated at the bottom right of FIG. 7, include a probe strand which is immobilized to a surface at one end and includes a label. Prior to cleavage, the probe strand also includes a selectively cleavable bond between the site of immobilization and the label. The probe strand can be hybridized to a corresponding target strand. The probe strand is cleaved by exposure to a cleaving solution. After cleavage, a double stranded structure remains in which one strand is cleaved and one remains uncleaved. See FIG. 7. The cleaved strand (e.g., the probe strand) can exist as two cleavage products. One cleavage product includes the label, but has no covalent attachment to the surface. The other cleavage product is without a label, but is covalently attached to the surface. The noncovalent hybridization between each cleavage product and different regions of the (uncleaved) target strand. By virtue of these noncovalent interactions, the labeled cleavage product remains immobilized with respect to the surface, even though there is no covalent interaction between the labeled cleavage product and the surface.

Comparing this structure to the one illustrated in Monforte '655 at FIG. 16, two differences are apparent: (i) both strands of the duplex oligonucleotide are cleaved, and (ii) a portion of the immobilized strand becomes mobile after cleavage. Stated more precisely, Monforte '655 does not describe a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. FIG. 16 shows one structure (i.e., 137) in which one strand (133) can be hybridized and immobilized (but is not

a cleavage product) and another structure (141 and 143 together) in which strand 133 has been cleaved, but the first cleavage product of this strand (the 3' end in FIG. 16) is not immobilized with respect to the surface.

Koster does not remedy this defect. Koster relates to DNA diagnostics based on mass spectrometry (see Title). In some embodiments Koster describes labels (e.g., M1, M2, and M3 in Figure 2) on detector oligonucleotides. See column 14, lines 14-30. The detector oligonucleotides are not cleavage products of a probe molecule. Rather, they are mass-modified oligonucleotides, synthetically prepared so as to hybridize to a selected sequence. Nothing in Koster teaches or suggests an array in which a first cleavage product of a first probe molecule is noncovalently immobilized with respect to the array surface.

With regard to independent claim 62, Monforte '655 does not teach two different probes on the array surface. The Examiner has indeed acknowledged this (Office Action at paragraph 10). Koster, while describing multiplexing, does not teach, suggest or provide motivation for an array having a cleavage product of a second probe molecule immobilized on the array surface. Koster simply does not describe the cleavage of an immobilized oligonucleotide strand.

Because the combined teachings of Monforte '655 in view of Koster do not teach, suggest or motivate a person of ordinary skill in the art to make a probe array having all the limitations of independent claims 1 or 62, Applicants respectfully ask that the rejection of these claims and those that depend from them be reconsidered and withdrawn.

Monforte '655 in view of Koster and Nikiforov

Claims 14 and 75 have been rejected as being obvious under 35 U.S.C. § 103(a) over Monforte '655 in view of Koster and U.S. Patent No. 5,518,900 to Nikiforov et al. ("Nikiforov"). Office Action at paragraph 11. Claim 14 depends from claim 1 and claim 75 from claim 62.

As discussed above, the combination of Monforte '655 with Koster fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is

noncovalently immobilized with respect to the array surface. Nikiforov does not remedy this defect.

Nikiforov is directed to nuclease resistant modified nucleotides, e.g., nucleotides including a phosphothioate linker. However, nothing in Nikiforov teaches, suggests, or provides motivation for a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Because Monforte '655 in view of Koster and Nikiforov does not teach all of the limitations of independent claims 1 and 62, Applicants respectfully seek reconsideration and withdrawal of the rejection.

Monforte '655 in view of Koster and Fung

Claims 16 and 77 have been rejected as being obvious over Monforte '655 in view of Koster and U.S. Patent No. 4,757,141 to Fung et al. ("Fung"). See the Office Action at paragraph 12. Claim 16 depends from claim 1; claim 77 depends from claim 62.

As discussed above, Monforte '655 in view of Koster fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Fung does not remedy this defect.

Fung is directed generally to amino-derivatized phosphite and phosphate linking agents (see Fung at Title). Nothing in Fung teaches, suggests, or motivates a person having ordinary skill in the art to make a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Applicants also respectfully disagree Fung teaches a detectable unit is coupled to probe molecules via an anchor group. The specification at page 40 describes that "the anchor groups are reacted with **specifically binding** components . . . which are detectable themselves or trigger a detectable reaction." The linking agents described in Fung do not engage in any specific binding. Rather, Fung teaches reagents that undergo covalent bond-forming reactions.

Because Monforte '655 in view of Koster and Fung does not teach all of the limitations of independent claims 1 and 62, Applicants respectfully seek reconsideration and withdrawal of the rejection.

Monforte '655 in view of Koster and Lockhart

Claims 17-18, 22-25, 78-79, and 83-86 have been rejected as being obvious over Monforte '655 in view of Koster and U.S. Patent No. 6,040,138 to Lockhart et al. ("Lockhart"). See the Office Action at paragraph 13. Claims 17-18 and 22-25 depend from claim 1; claims 78-79 and 83-86 depend from claim 62.

As discussed above, Monforte '655 in view of Koster fails to teach all the limitations of independent claim 1. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Lockhart does not remedy this defect.

Regarding claims 1 and 62, Lockhart teaches that only the non-immobilized member of a hybridized pair (i.e., the target) of nucleic acids carries a label. Lockhart does not describe any immobilized, labeled probes. See Lockhart, for example, at column 13, line 36 to column 14, line 36 (section titled "Labeling Nucleic Acids") describing, *inter alia*, that "'direct labels' . . . are directly attached to or incorporated into the target (sample) nucleic acid prior to hybridization. In contrast, 'indirect labels' are joined to the hybrid duplex after hybridization." Column 14, lines 16-20. In both cases, the label is never associated with an immobilized probe. The Examiner "agrees that **Lockhart does not teach the labeled probes are immobilized**; however, Lockhart is relied upon solely for the additional third, fourth, and fifth probes of the array." See the Office Action at "Response to Arguments," page 26 (emphasis added).

Independent claims 1 and 62 each relate to probe arrays in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.. As described immediately above, **Lockhart does not teach the labeled probes are immobilized**, a point which the Examiner has conceded. Accordingly, the combination of teachings of Monforte and Lockhart fails to teach each and every element of

independent claims 1 and 62. As such, there is no *prima facie* case of obviousness. Applicants therefore respectfully ask that the Examiner reconsider and withdraw the rejection of independent claims 1 and 62 and the claims that depend from them.

Mackay

Claims 19 and 80 have been rejected as being obvious over Monforte '655 in view of Koster and U.S. Patent No. 5,700,642 to Mackay ("Mackay"). See the Office Action at paragraph 14. Claim 19 depends from claim 1 and claim 80 from claim 62.

As discussed above, Monforte '655 in view of Koster fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Mackay does not remedy this defect.

Mackay is directed to visualization of spots in an electrophoretic gel using a charge-coupled device (see Mackay at Abstract). Nothing in Mackay teaches, suggests, or motivates a person having ordinary skill in the art to make probe array having in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

In addition, Mackay does not teach a cleavage product of a probe molecule immobilized on an array surface at a defined site. Instead, Mackay relates to visualization of spots in an electrophoretic gel, a technique which requires that the molecules to be detected are mobile and not immobilized.

For at least the reasons given, Monforte '655 in view of Koster and Mackay does not teach all the limitations of claims 1, 19, 62 and 80. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

Monforte '655 in view of Koster, Lockhart and Kievits

Claims 20 and 81 has been rejected as being obvious over Monforte '655 in view of Koster, Lockhart and U.S. Patent No. 5,770,360 to Kievits et al. ("Kievits"). See the Office Action at paragraph 15.

As discussed above, Monforte '655 in view of Koster fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Kievits (alone or in combination with Lockhart) does not remedy this defect.

Kievits is directed to elimination of false negatives in detection of amplified nucleic acids. Nothing in Kievtis teaches, suggests, or motivates a person having ordinary skill in the art to make probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Applicants maintain their previous argument that Kievits does not teach the limitation for which it is cited. The Examiner argues that Kievits teaches probe molecules "which differ in their labeling degree (e.g., the probes are labeled differently [column 5, lines 32-37]; therefore the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe)." See the Office Action at page 11. Applicants respectfully disagree. The specification explains how probes differ in their degree of labeling "for example with a defined mixture of labeled and unlabelled probes varying in the form of a dilution series from array element to array element." In order to normalize a measurement, "the values of the detection standard elements . . . are plotted against the mixing ratio of labeled and unlabelled substance. This results in a calibration curve which indicates the dynamic range and the type of interdependence between the quantity of detectable units." (specification at 58-59).

The relevant portion of Kievits reads:

> In order to detect whether the analyte or the internal control is bound to the solid phase, two differently labeled detection probes now can be used. One will react specifically with the analyte bound to the solid phase . . . while **the second labeled detection probe, comprising a label that can be distinguished from the label on the first detection probe**, will react specifically with the internal control. The internal control used in this case

> must resemble the analyte in its capability of hybridizing to the immobilized oligonucleotide on the solid phase, but must differ from the analyte in that it will react with a different labeled detection probe than the analyte.

Kievits at column 5, lines 24-37 (emphasis added). **Kievits teaches a difference in kind—the labels can be distinguished from one another—not a difference in degree**. Claims 20 and 81 relate to probe arrays in which different array elements differ in their **labeling degree**, a feature not taught by Kievits, or by the combination of references.

For at least the reasons given, Monforte '655 in view of Koster, Lockhart and Kievits do not teach all the limitations of claims 20 and 81. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

Monforte '655 in view of Koster, Mackay and Kievits

Claims 21 and 82 have been rejected as being obvious over Monforte '655 in view of Koster, Mackay and Kievits. See the Office Action at paragraph 16.

As discussed above, Monforte in view of Koster fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte '655 in view of Koster does not teach a probe array in which the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. Kievits (alone or in combination with Mackay) does not remedy this defect.

Kievits is directed to elimination of false negatives in detection of amplified nucleic acids. Nothing in Kievits teaches, suggests, or motivates a person having ordinary skill in the art to make probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Furthermore, as discussed above, Kievits does not teach detectable units arranged on different array elements which differ in their labelling degree.

For at least the reasons given, Monforte '655 in view of Koster, Mackay and Kievits do not teach all the limitations of claims 21 and 82. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants ask that all claims be allowed. If the Examiner believes it to be helpful, the Examiner is invited to contact the undersigned representative by telephone at 202-429-3000. A petition for a two-month extension of time is enclosed with this reply. Please apply any charges or credits to deposit account 19-4293.

Respectfully submitted,

Date: 7.7.08

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